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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,849	02/27/2002	Tamar H. Michaeli	96700/733	3506

7590 03/08/2004

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EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,849	MICHAELI, TAMAR H.	
	Examiner	Art Unit	
	Michele C. Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 3, 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11 and 13-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on December 3, 2003. Acknowledgment is made of Applicant's cancellation of Claims 1-9 and 12.

Claims 10, 11 and 13-19 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-19 as amended are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing glucose dependent insulin secretion in a pancreatic β-cell of a mammal, wherein the mammal is need of increased glucose dependent insulin secretion, the method comprising administering an effective amount of a selective inhibitor of phosphodiesterase 1C to a mammal in need thereof, does not reasonably provide enablement for a method of increasing glucose dependent insulin in a pancreatic β-cell in a mammal in need thereof comprising administering any and all amounts of phosphodiesterase 1C to the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Newly applied as necessitated by amendment.

The claims are directed to a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, where the mammal is in need of increased glucose dependent insulin secretion, the method comprising administering a selective inhibitor of phosphodiesterase 1C.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2D 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

While Applicant has reasonably demonstrated a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal comprising administering an effective amount of either zaprinast or 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX) to the pancreatic β-cell of a mouse, *i.e.*, TC3 cells, Applicant has not demonstrated a method of increasing glucose dependent insulin secretion in a mammalian pancreatic β-cell, the method comprising administering any and/or all amounts of a selective inhibitor of phosphodiesterase 1C to a mammal in need of increased glucose dependent insulin secretion, as broadly claimed by Applicant. For instance, on page 24, lines 1-16, Applicant discloses effective dose

range amounts for the administration of selective phosphodiesterase 1C inhibitors to mammals in need thereof to provide the claimed beneficial effect for insulin secretion.

Moreover, it should be noted that the state of the art at the time of filing neither teaches the claim-designated ingredients of Claim 13, *e.g.,* zaprinast, 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX), vinpocetine, rolipram, and milrinone, as phosphodiesterase inhibitors of 1C nor as having the claimed beneficial functional effect for increasing glucose dependent insulin secretion in a mammalian pancreatic β-cell comprising the administration of any and/or all amounts a inhibitor phosphodiesterase 1C to a mammal in need thereof of such treatment. Firstly, on page 1488, Column 2, lines 11-23, Shafiee-Nick (18, Shafiee-Nick et al., British Journal of Pharmacology, 1995. 115(8): 1486-1492. *Effects of Type-Selective Phosphodiesterase Inhibitors on Glucose-Induced Insulin Secretion and Islet Phosphodiesterase Activity".*) teaches, "At concentrations up to 10^{-3} M zaprinast did not modify glucose-induced insulin secretion, whereas at 10^{-3} M but not at 10^{-4} M, rolipram was inhibitory (insulin secretion, μu/islet h^{-1}; control 58.4 ± 2.8 (*n*=36), rolipram 10^{-3} M 26.3 ± 3 (*n*=24); *P*<0.01). Pre-incubation of islets (30 min) with zaprinast followed by incubation with the drug (60 min) resulted in a concentration-dependent inhibition of glucose-insulin release (insulin secretion, zaprinast 10^{-6} M 51.8 ± 2 (*n*=10, NS); 10^{-5} M 41.6 ± 2.4 (*n*=9, *P*<0.05); 10^{-4} M 30.5± 5.3 (*n*=8, *P* < 0.01). Rolipram inhibited insulin secretion to 33 ± 1 μu/islet h^{-1} (*P* < 0.01) at 10^{-4} M (10 fold lower than previously) when preincubated (followed by incubation) with islets." Note that on page 1489, Column 2, lines 10-28, Shafiee-Nick teaches that rolipram had no inhibitory effect on cyclic AMP-PDE activity in some instances, whereas

in others rolipram inhibited cyclic AMP-PDE activity up to 20%; and, that zaprinast did not consistently inhibit cyclic AMP-PDE activity. Moreover, Shafiee-Nick does not teach either rolipram or zaprinast as inhibitors of phosphodiesterase 1C; although, on page 1491, Column 1, lines 30-33, Shafiee-Nick does suggest the identification of rolipram as a type I PDE. For instance, Shafiee-Nick teaches, "Zaprinast, an inhibitor of both type I and type V PDEs, failed to enhance insulin release when incubated with the islets and actually inhibited secretion following preincubation", on page 1490, Column 2, line 65 bridging page 1491, line 11. Finally, Shafiee-Nick teaches rolipram as a type IV PDE inhibitor. *See* abstract. Secondly, Clarke (V, Clarke et al., Pulmonary Pharmacology, 1994, 7: 81-89. *The Type III Phosphodiesterase Inhibitor Milrinone and Type V PDE Inhibitor Dipyridamole Individually and Synergistically Reduce Elevated Pulmonary Vascular Resistance"*) teaches milrinone as a Type III phosphodiesterase inhibitor, and zaprinast as a Type V phosphodiesterase inhibitor. Even Applicant readily admits that milrinone mediates dual inhibitory specificity for PDEs in cultured pancreatic β-cells, on page 43, lines 16-23. Furthermore, Applicant readily admits, "Selective inhibition of PDE3B in cultured pancreatic β-cells by milrinone when assayed with limited excess over the IC_{50} does not augment glucose induced insulin secretion but counteracts IDF-1 and leptin inhibition of insulin secretion [citations omitted]." Thus, while Applicant claims a method of increasing glucose dependent insulin in a pancreatic β-cell in a mammal in need thereof, wherein the method comprises administering any and/or all amounts of a selective inhibitor of phosphodiesterase 1C to the mammal, the art at the time of filing of

the instantly claimed invention suggests that the administration of the claim-designated ingredients failed to exhibit the claimed beneficial functional effect.

Inventions targeted for insulin secretion/diabetes therapy bear a responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. Moreover, effective treatments for treating such disease conditions are relatively complicated, and may be unbelievable in the absence of supporting evidence. Claims drawn to methods intended for the administration of compounds to mammalian pancreatic β-cells, especially wherein the mammal is human, for increasing glucose dependent insulin secretion in the pancreatic β-cells of a mammal in need of such a treatment, generally require supporting evidence which clearly define the ingredients or constituents contained therein and the effective amounts of the ingredients to provide the claimed functional effect because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the therapeutic effective amounts of the claim-designated compositions that are to be administered to a human. There is no guidance in the specification, other than the demonstrated method of increasing glucose dependent insulin secretion in a pancreatic β-cell of a mouse (a well accepted mouse model, *i.e.*, β-TC3 cell model, for research study on drug therapy for diabetic humans) comprising the administration of effective amounts of a selective inhibitor of phosphodiesterase 1 C to a mammal in need of increased glucose dependent insulin secretion.

Given the insufficient guidance in the specification as to how to carry out the instantly claimed invention for the proposed method of therapeutic treatment, the lack of working examples, and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

According, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed selective inhibitors of phosphodiesterase 1C would have the claimed functional effect for increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal , the method comprising administering any and/or all amounts of a selective inhibitor of phosphodiesterase 1C to a mammal in need of increased glucose dependent insulin secretion, other than the aforementioned demonstrated method of increasing glucose dependent insulin secretion in a mammalian pancreatic β-cell comprising administration of effective amounts of the claim-designated inhibitors of phosphodiesterase 1C.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 11 and 13 as amended and Claim 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Parker et al. (U). Newly applied as necessitated by amendment.

Applicant claims a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, where the mammal is in need of increased glucose dependent insulin secretion, the method comprising administering a selective inhibitor of phosphodiesterase 1C to the mammal. Applicant further claims the method of Claim 10, wherein the inhibitor is an isobutylmethylxanthine with substitutions consisting of a moiety at positions 2 (R1) and 8 (R2) independently selected from the group consisting of an alkyl (C_1 to C_3), a flouroalkyl (F_1 to F_3), a chloroalkyl (Cl_1 to Cl_3), an aryl (C_5 to C_6), a fluoroaryl (F_1 to F_2), and a chloroaryl (Cl_1 to Cl_2). Applicant further claims the method of claim 10, wherein the inhibitor is selected from the group consisting of zaprinast, 8-methoxymethyl-1-3-(2-methylpropyl)xanthine (8MM-IBMX), vinpocetine, rolipram, milrinone, and combinations thereof. Applicant further claims the method of claim 10, wherein the inhibitor is administered orally.

Parker teaches a method of increasing glucose dependent insulin secretion in mice comprising the oral administration of an effective amount of milrinone to diabetic ob/ob mice, on page 666, Column 2, lines 7-14. *See* Figure 1, also. Parker does not teach her method as a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal *per se* comprising administering a selective inhibitor of phosphodiesterase 1C to the mammal, *i.e.*, Parker does not teach milrinone as a selective inhibitor of phosphodiesterase 1C. However, the instantly claimed process is

a one-step process of increasing glucose dependent secretion in a pancreatic β-cell in a mammal, wherein the mammal is in need of increased glucose dependent insulin secretion, the method comprising orally administering milrinone to the mammal, which is defined as an inhibitor of phosphodiesterase 1C. Thus, the functional effect of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal in need thereof comprising the oral administration of an inhibitor of phosphodiesterase 1C is inherent to the method of administering the milrinone composition to the diabetic ob/ob mice taught by Parker, since the method step and the ingredient are the same as instantly claimed by Applicant. Furthermore, the Office notes that Applicant readily admits, on page 43, lines 8-23, that milrinone has dual specificity as a PDE1C and PDE3 inhibitor in a mammalian pancreatic β-cell.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10, 11 and 13 as amended and Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parker et al. (U) and in view of Weiner et al. (C), Bhagwart et al. (B) and Bosies et al. (A). Newly applied as necessitated by amendment.

Applicant's claimed invention of Claims 10, 11, 13 and 18 was set forth above. Applicant further claims the method of claim 10, wherein the mammal is human; wherein the inhibitor is administered in an effective amount to regulate blood sugar levels in the mammal; and, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide.

The teachings of Parker are set forth above. Parker does not teach a method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal; and, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the phosphodiesterase inhibitor taught by Parker in a method of increasing glucose dependent insulin secretion in a pancreatic-β-cell in a mammal comprising administering the milrinone to a mammal in need thereof to provide the instantly claimed invention because Parker teaches the beneficial functional effect of the claim-designated ingredient on the secretion of insulin in diabetic ob/ob mice. One of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of increasing glucose insulin secretion in a pancreatic β-cell taught by Parker by administering the referenced milrinone to a mammal because, at the time the invention was made, the use of a diabetic ob/ob mouse assay as a test for the determination of mammal and/or human

drug therapy for the treatment of diabetes was well-documented and widely accepted. Moreover, Parker clearly teaches that cyclic AMP phosphodiesterase inhibitors, such as milrinone, are effective insulin secretagogues.

With regard to Claim 17 wherein Applicant further claims a method wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal, the Office notes that Parker suggests that the referenced phosphodiesterase, namely milrinone, may have limited therapeutic utility for human diabetic subjects because of its concurrent stimulation of lipolysis and hepatic glucose output. Yet, Parker also teaches, "However, it was only in the *ob/ob* mouse, an animal model of extreme hyperinsulinemia and insulin resistance [citation omitted], that these effects caused an increase in blood glucose; in their lean littermates glucose tolerance was improved. It may be that human diabetic subjects, who typically exhibit a far less extreme constellation of symptoms than that seen in the *ob/ob* mouse and whose disease can often be satisfactorily treated by therapeutic agents such as the sulfonylureas that are ineffective in that animal model, may benefit from treatment with appropriately selective inhibitors of PDE III." Thus, while Parker identifies milrinone as an inhibitor of PDE III, instead of a selective inhibitor of PDE 1C, Parker does suggest the use of milrinone as an anti-diabetic agent for treatment of humans. Thus, at the time the invention was made, it would have been obvious to one of ordinary skill in the art and one would have been motivated and one would have had a reasonable expectation of success to optimize the method of administering the milrinone taught by Parker to regulate blood sugar levels in a mammal by varying the dose amounts of the

drug taught by Parker to provide the claim-designated functional effect because Parker clearly suggests the beneficial treatment administration of phosphodiesterases to humans to increase insulin secretion without deleterious effects on glucose levels. *See* page 667 to page 669, under "DISCUSSION". Thus, the effective varying amounts of the dose administration of the milrinone taught by Parker would have been merely a matter of routine experimentation for one of ordinary skill in the art at the time the invention was made to provide the claimed functional effect to regulate blood sugar levels in a mammal, such as a human, since Parker teaches that the administration of milrinone to lean mice increased insulin levels and improved glucose tolerance, on page 666, Column 2, lines 7-24.

With regard to Claim 19 wherein Applicant claims a method wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide, it would have been obvious to one of ordinary skill in the art to add the instantly claimed ingredients to the modified method taught by Parker set forth immediately above because at the time the invention was made the administration of insulin, sulfonylurea and biguanide as anti-diabetic agents was well known in the art, as evidenced by the teachings of Weiner, Bhagwart and Bosies. Firstly, Weiner teaches a method of treating diabetes comprising the oral administration of an analog of insulin to a mammal. Secondly, Bhagwart teaches a method of treating diabetes comprising orally administering a therapeutic effective amount of a sulfonylurea in a sustained release dosage. Thirdly, Bosies teaches a biguanide composition which is suitable for oral administration in the treatment of

diabetes. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add the instantly claimed ingredients to the method of increasing insulin secretion by treating a pancreatic β-cell with the inhibitor of phosphodiesterase 1C taught by the modified method of treatment taught by Parker to provide the claimed invention because in the patent claims, Weiner teaches that the oral administration of the insulin analog of his method is useful in treating diabetes, suppressing autoimmune response against pancreatic beta cells and maintaining at least partial pancreatic beta cell function in a mammal without causing a decrease in blood sugar level in a mammal; and, thus, the regulation of blood sugar levels in a mammal; in Column 4, lines 27-40, Bhagwart teaches that the referenced controlled release sulfonylurea is suitable for once-a-day or 24 hour administration, is economical and convenient for the treatment of diabetes; and, in the abstract, Bosies teaches that treatment of diabetes mellitus with the referenced anti-diabetic biguanide composition lacks the typical side effects of biguanide treatment, *viz.*, lactacidosis.

Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add any of the claimed ingredients in the making of the claimed methods because it is well known that its *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten,* 459 F. 2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi,* 58

CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett,* 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). Thus, at the time the invention was one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add any of the claimed ingredients taught by either Weiner, Bhagwart or Bosies to the modified method of increasing insulin secretion in diabetic ob/ob mice taught by Parker to provide the claimed method because the claimed invention is no more than the combining of well known ingredients used in well known methods for increasing insulin secretion in a pancreatic β-cell in a mammal and/or a human.

Accordingly, the claimed invention was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele C. Flood whose telephone number is (571) 272-0964. The examiner can normally be reached on 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MCF
March 5, 2004

CHRISTOPHER R. TATE
PRIMARY EXAMINER